

# Stability of Lansoprazole in Extemporaneously Compounded Suspensions for Nasogastric or Oral Administration

Mary H H Ensom, Diane Decarie, and Ian Sheppard

## ABSTRACT

**Objective:** To evaluate the stability of extemporaneously compounded lansoprazole suspensions for nasogastric or oral administration after storage at 4°C and 25°C for up to 91 days.

**Methods:** Suspensions of lansoprazole 3 mg/mL in 8.4% sodium bicarbonate (for nasogastric administration) and of lansoprazole 3 mg/mL in 8.4% sodium bicarbonate in a 1:1 mixture of Ora-Sweet sweetening agent and Ora-Plus suspending agent buffered with 1N sodium hydroxide (for oral administration) were prepared in 50-mL amber glass prescription bottles. Three bottles of each suspension were stored at 4°C (refrigerated), and 3 were stored at 25°C (room temperature). The physical characteristics of pH, odour, and taste were evaluated weekly for 91 days, and colour, precipitation, and ease of resuspension were determined by visual testing at the same intervals. Aliquots were removed from each bottle weekly for 91 days and stored at -85°C until analysis by a validated high-performance liquid chromatography method. A suspension was considered stable if it maintained 90% of its initial concentration.

**Results:** No notable changes in pH, odour, or colour were observed in suspensions of either the nasogastric or the oral formulation after storage at 4°C or 25°C for 91 days. The taste of the oral suspensions remained essentially the same over the 91-day period; the nasogastric suspension developed a more bitter taste by day 49, but this altered taste then remained stable until the end of the study. Precipitates were easily resuspended, and there was no caking or clumping of material. Both the nasogastric and the oral formulations maintained more than 90% of the initial lansoprazole concentration on day 91. The calculated lower limit of the 95% confidence interval also indicated that 90% (specifically, 89.64%) or more of the initial concentration remained on day 91.

**Conclusions:** Extemporaneously prepared lansoprazole suspensions (nasogastric and oral) were stable for a period of up to 91 days, with or without refrigeration. Because stability alone cannot guarantee bioavailability or efficacy, additional clinical studies are recommended to evaluate the pharmacokinetics and pharmacodynamics of these formulations.

## RÉSUMÉ

**Objectif :** Évaluer la stabilité des préparations extemporanées de lansoprazole en suspension pour l'administration par sonde nasogastrique ou par voie orale, qui ont été entreposées à 4 °C et à 25 °C pendant une période allant jusqu'à 91 jours.

**Méthodes :** Les suspensions de lansoprazole à 3 mg/mL dans du bicarbonate de sodium à 8,4 % (pour administration par sonde nasogastrique) et les suspensions de lansoprazole à 3 mg/mL dans du bicarbonate de sodium à 8,4 % dans un mélange 1:1 d'Ora-Sweet (édulcorant) et d'Ora-Plus (agent de suspension) tamponné avec de l'hydroxyde de sodium 1N (pour administration par voie orale) ont été préparées dans des flacons d'ordonnance de 50 mL de verre ambré. Trois flacons de chaque suspension ont été entreposés à 4 °C (au réfrigérateur), et trois autres ont été entreposés à 25 °C (à la température ambiante). On a évalué les caractéristiques physiques, notamment le pH, l'odeur et le goût, toutes les semaines pendant une période de 91 jours, et une inspection visuelle aux mêmes intervalles a servi à déterminer la couleur, la formation de précipité et la facilité de remise en suspension. Des aliquotes ont été prélevées de chaque bouteille toutes les semaines pendant une période de 91 jours, puis entreposées à -85 °C jusqu'à ce qu'elles soient analysées par chromatographie liquide à haute pression. La suspension était considérée comme stable si elle conservait 90 % de sa concentration initiale.

**Résultats :** Aucun changement notable de pH, d'odeur ou de couleur n'a été noté dans les suspensions pour administration par sonde nasogastrique ou par voie orale après une période d'entreposage de 91 jours à 4 °C ou à 25 °C. Le goût des suspensions pour l'administration par voie orale est demeuré essentiellement le même pendant la période de 91 jours; la suspension pour administration par sonde nasogastrique a développé un goût plus amer au jour 49, qui est demeuré le même jusqu'à la fin de l'étude. Les précipités ont été remis en suspension facilement, et on n'a observé aucune agglutination des composants. Les préparations pour l'administration par sonde nasogastrique et par voie orale ont toutes deux conservé plus de 90 % de leurs concentrations initiales de lansoprazole au jour 91. La limite inférieure de l'intervalle de confiance à 95 % indiquait



**Key words:** high-performance liquid chromatography, proton pump inhibitors, pediatrics

---

Can J Hosp Pharm 2007;60(3):184-191

---

## INTRODUCTION

The proton pump inhibitor lansoprazole is widely used in adults to treat ulcers, gastroesophageal reflux disease (GERD), and conditions in which the stomach produces excessive acid (e.g., Zollinger-Ellison syndrome).<sup>1,2</sup> In February 2005, lansoprazole was approved by Health Canada for pediatric GERD.<sup>3</sup> Unfortunately, no liquid dosage form is commercially available in Canada, and no product of this type is expected in the short term.<sup>4</sup>

Extemporaneously compounded suspensions of lansoprazole present particular problems.<sup>5-11</sup> This drug, a weak base, is acid labile and thus typically administered (for patients who are able to swallow capsules) as capsules of enteric-coated granules. The protective gelatin capsules are used because the enteric coating dissolves at pH above 6 (i.e., the pH of water and saliva). Gastric acid subsequently dissolves the capsules, a process that releases the granules into the stomach. The low pH of the stomach prevents dissolution of the enteric coating until lansoprazole reaches the more alkaline small intestine for absorption.<sup>5</sup> For patients who receive lansoprazole via nasogastric tube, the granules have typically been suspended in sodium bicarbonate (NaHCO<sub>3</sub>).<sup>6</sup> The rationale for suspension in 8.4% NaHCO<sub>3</sub> is 2-fold. First, dissolution of the enteric coating is necessary in order for the mixture to flow through the tube, since intact granules may block the tube, especially the smaller ones that might be used in children. Second, an alkaline suspension is required to neutralize gastric acid and thus maintain a neutral milieu and prevent intraluminal protonation and degradation of the lansoprazole. Despite a number of reports involving lansoprazole suspensions prepared in 8.4% NaHCO<sub>3</sub>,<sup>5-11</sup> no documentation could be found regarding expiration dates longer than 4 weeks.<sup>7</sup>

également que les préparations avaient conservé 90 % (89,64 % précisément) ou plus de leurs concentrations initiales au jour 91.

**Conclusions :** Les préparations extemporanées de lansoprazole en suspension (pour administration par sonde nasogastrique et par voie orale) sont demeurées stables pendant une période allant jusqu'à 91 jours, qu'elles aient été réfrigérées ou non. Comme la stabilité seule ne peut garantir la biodisponibilité ou l'efficacité du médicament, d'autres études cliniques sont recommandées afin d'évaluer le comportement pharmacocinétique et pharmacodynamique de ces préparations.

**Mots clés :** chromatographie liquide à haute pression, inhibiteurs de la pompe à protons; pédiatrie

Unfortunately, although lansoprazole in 8.4% NaHCO<sub>3</sub> is acceptable for nasogastric use, it is unpalatable for oral administration. Palatability is a significant issue, particularly for children. This study took advantage of the improved palatability of lansoprazole in commercially available sweetening and suspending agents Ora-Sweet and Ora-Plus, respectively, and took into account the rationale underlying use of an alkaline suspension in the preparation of a palatable suspension for oral administration.

The purpose of the study reported here was to evaluate the stability of extemporaneously compounded lansoprazole suspensions for nasogastric or oral administration after storage at 4°C and 25°C in glass bottles for up to 91 days.

## METHODS

### Pretesting Experiments for Oral Suspension

Because palatability is an issue with oral suspensions, preliminary experiments were conducted to ensure that the final oral formulation would not only meet alkaline pH criteria but also be palatable.

Three oral formulations were pretested. The formulations for suspensions 1 and 2 are presented in Appendix 1. The formulation for suspension 3, also presented in Appendix 1, was identical with that of 2, except it was buffered to an alkaline pH of about 8.4 with NaHCO<sub>3</sub> instead of sodium hydroxide (NaOH). All 3 formulations were subjected to a blinded, randomized crossover taste test by 9 adult volunteers (pharmacy department employees). Each taster was blinded to the composition of each formulation as well as to the other tasters' ratings. There was 100% congruence between testers: all 9 testers ranked suspension 2 as best and found it palatable; suspension 1 was ranked worst and was



deemed unpalatable by all testers; and suspension 3 was ranked second by all testers, 5 of whom deemed it unpalatable and 4 of whom deemed it palatable. Although suspension 1 was not palatable, the palatability of a nasogastric formulation is not a major issue. Thus, suspension 1 was selected as the nasogastric formulation to avoid any potential problems with clogging of tubes.

### Preparation of Nasogastric and Oral Suspensions

The first set of samples (the nasogastric suspension; suspension 1) was prepared by mixing the contents of commercially available 30-mg capsules of lansoprazole (Abbott Laboratories, Saint-Laurent, Quebec; lot 328062E2, expiry date December 2008) in 8.4% NaHCO<sub>3</sub> (made from powder chemical available from Medisca Pharmaceutique Inc, Montréal, Quebec; lot 1253WB, no expiry date) to a final concentration of 3 mg/mL, pH 8.4 (Appendix 1). The second set of samples (an oral suspension; suspension 2) was prepared by mixing 150 mL of lansoprazole (6 mg/mL in 8.4% NaHCO<sub>3</sub>) and 150 mL of a 1:1 mixture of Ora-Sweet sweetening agent and Ora-Plus suspending agent (Paddock Laboratories Inc, Minneapolis, Minnesota; lots 5023028 and 5153778 with expiry dates October 2007 and March 2007, respectively), buffered with 1N NaOH (Fisher Scientific, Nepean, Ontario; lot SC9105042) to a final concentration of 3 mg/mL, pH 8.4. (Appendix 1). Six 50-mL replicates of each set of samples were prepared in separate 100-mL amber glass prescription bottles (Richards Distribution, Richmond, British Columbia); 3 bottles from each set were stored at 4°C (refrigerated) and 3 were stored at 25°C (room temperature). All bottles were exposed only to fluorescent lighting in the laboratory.

The physical characteristics of the suspensions were evaluated qualitatively at the time of preparation and at weekly intervals up to 91 days. As samples were collected during the 91-day study period, all suspensions were tested by the same individual for odour and taste and were visually examined for changes in colour (against white and black backgrounds), formation of precipitate, and ease of resuspension. The glass bottles containing the samples were allowed to equilibrate to 25°C and were then shaken manually for 10 s; the pH was determined from the suspension remaining in each bottle. The pH meter (model 8000, VWR Canlab, Mississauga, Ontario) was calibrated with commercially available standards at the beginning of each testing session. Immediately after the physical observations, samples were obtained (in 2-mL polypropylene vials, VWR, Edmonton, Alberta) and immediately stored at -85°C until analyzed by a stability-

indicating high-performance liquid chromatography (HPLC) method with ultraviolet (UV) detection, as developed in the authors' laboratory on the basis of previously published reports.<sup>6,9,12</sup>

### Preparation of Stocks and Standards and Preparation of Standard Curve

Lansoprazole (in the form of 30-mg capsules) prepared to a final concentration of 3 mg/mL in NaHCO<sub>3</sub> (pH 8.4) was used to prepare the stock solutions. Standards were prepared as follows: lansoprazole 3 mg/mL was mixed 1:3 in HPLC-grade methanol (Fisher Scientific, Richmond, British Columbia; lot B 1562) and subjected to centrifugation at 3000 rpm for 3 min. The supernatant was diluted in HPLC-grade water (Fisher Scientific, Richmond, British Columbia; lot 055941) to final concentrations of 200, 400, 600, 800, and 1000 µg/mL to construct the standard curve. The internal standard was prepared by dilution of injectable pantoprazole (Altma Laboratories, Oakville, Ontario; lot 458021) in HPLC-grade water to a concentration of 40 µg/mL. Standards were prepared by combining 0.1 mL of each stock, 0.4 mL of HPLC-grade water, and a 0.5-mL aliquot of pantoprazole 40 µg/mL. The final concentrations of lansoprazole in the standard samples injected onto the chromatograph were 20, 40, 60, 80, and 100 µg/mL. The final concentration of internal standard (pantoprazole) was 20 µg/mL. These dilutions achieved optimal chromatographic characteristics. Before injection, all standards were passed through a 0.45-µm microfilter (Acrodisc GHP syringe filter, Gelman, Ann Arbor, Michigan; lot 10434502) to prevent injection of impurities onto the column.

A 5-point calibration curve was prepared with a blank (water only) at the beginning of each run, to ensure that there was no carry-over from one run to the next. The range of this calibration curve (20 to 100 µg/mL) encompassed the diluted (30 µg/mL) test concentration of lansoprazole 3 mg/mL. The calibration curve was generated by least-squares regression of the peak area ratio of lansoprazole to pantoprazole (standard) and the concentration of each (lansoprazole) standard. The precision of the assay was evaluated by intraday and interday validation methods. Intraday variability was determined by running stock solutions of 200, 400, 600, and 800 µg/mL (diluted to standards of 20, 40, 60, and 80 µg/mL) in quadruplicate throughout a single day, and interday variability was determined by running the same concentrations (as in the testing for intraday variability) in quadruplicate daily for 4 days. The means, standard deviations, and coefficients of variation were then calculated. Acceptable limits for the coefficients of variation were defined a priori as less than 10%.



## Preparation of Samples

Lansoprazole study samples were thawed and mixed (vortexed for 10 seconds), and a 0.1-mL aliquot was diluted with 0.9 mL of HPLC-grade methanol and centrifuged for 3 min at 3000 rpm. A 0.1-mL aliquot of the supernatant (lansoprazole) was added to a 0.9-mL aliquot of HPLC-grade water containing the internal standard. The final theoretical lansoprazole concentration was 30 µg/mL. Each sample was passed through a 0.45-µm microfilter before a 50-µL sample was withdrawn and injected onto the column.

## HPLC Instrumentation

The HPLC instrumentation (model 2690, Waters Alliance Systems, Waters Ltd, Mississauga, Ontario) consisted of a delivery pump, an automatic injector equipped with a 200-mL injector, an XTerra RP (reverse-phase) C<sub>18</sub> 4.6 x 100 mm column (Waters Ltd, lot W20081T021), and a UV detector set at 225 nm (model 2487 dual-wavelength absorbance detector, Waters Ltd). The mobile phase consisted of a 26:74 (v/v) mixture of acetonitrile (Fisher Scientific, Richmond, British Columbia; lot B1062) and a 50 mmol/L solution of Na<sub>2</sub>HPO<sub>4</sub> (Sigma-Aldrich, Oakville, Ontario; lot 19H0245), pH 10. All solvents were HPLC grade and were filtered before use. The flow rate was set at 1.75 mL/min.

## Degradation of Lansoprazole

Lansoprazole 1 mg/mL, made from 3 mg/mL standard, was incubated overnight for 18 h at 60°C. The 3-mL sample was then cooled to 25°C. The pH was adjusted to 0.1 with 10N HCl and was readjusted to pH 8.4 with 12N NaOH. The sample was then adjusted with water to a final concentration of 60 µg/mL (containing 20 µg/mL of the internal standard, pantoprazole) and filtered, and a 50-µL sample was injected onto the column. The chromatogram obtained for the degraded preparation was compared with a chromatogram obtained from a 60 µg/mL standard to determine any changes in concentration, retention time, and peak shape.

## Statistical Analysis

The means, standard deviations, and coefficients of variation were calculated for samples analyzed in triplicate and quadruplicate. For each study day, the percentage of initial lansoprazole concentration remaining was calculated for each sample. The percentage of lansoprazole remaining on day 91 was calculated from the concentration on day 91 as determined by linear regression and the concentration observed on day zero,

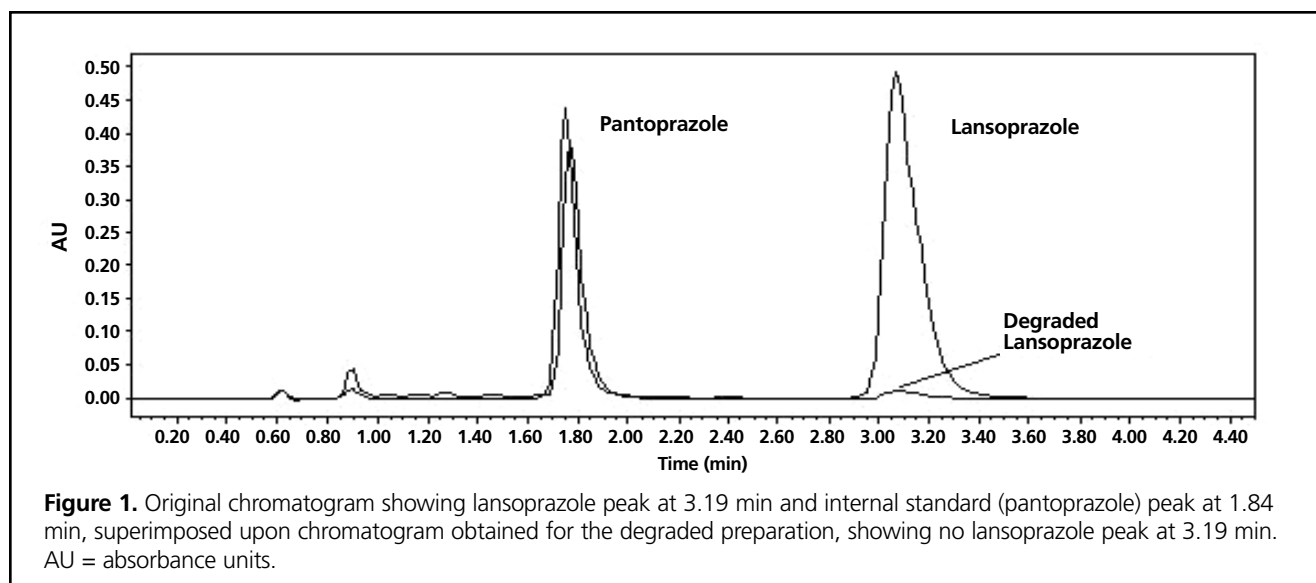
according to the following formula: concentration on day 91/concentration on day zero x 100%. The 95% confidence interval (CI) of the amount remaining on the last study day was calculated from the lower limit of the 95% CI of the slope of the curve relating concentration to time, determined by linear regression, obtained by computer analysis (SPSS 12.0 for Windows, Chicago, Illinois), according to the following formula: lower limit of the 95% CI of the concentration on day 91/concentration on day zero x 100%. Stability was defined as maintenance of at least 90% of the initial lansoprazole concentration.

## RESULTS

For the standard curve generated, regression analysis of the peak area ratio of lansoprazole (standards) to internal standard versus concentration demonstrated linearity over the working range of the standard concentrations, with coefficients of determination (*r*<sup>2</sup>) greater than 0.993 (*n* = 4). The intraday (*n* = 4) and interday (*n* = 4) coefficients of variation for the 4 different concentrations of standards were within acceptable limits (i.e., less than 10%): 1.74% and 0.86%, respectively, for the 20 µg/mL suspension, 5.01% and 1.19%, respectively, for the 40 µg/mL suspension; 0.26% and 1.04%, respectively, for the 60 µg/mL suspension; and 0.30% and 2.69%, respectively, for the 80 µg/mL suspension.

The retention time for lansoprazole was 3.19 min, whereas the retention time for the internal standard, pantoprazole, was 1.84 min (Figure 1). When lansoprazole was subjected to degradation, the lansoprazole peak virtually disappeared, and no significant peak (of lansoprazole) was observed at 3.19 min (Figure 1). Thus, the HPLC method was deemed capable of indicating stability.

Each cloudy, white suspension had either a neutral (nasogastric formulation) or a faintly sweet (oral formulation) smell and either a salty or a sweet-and-salty taste, respectively. No notable changes in physical appearance, odour, or colour of the suspensions were observed over a period of 91 days. Although the oral suspension maintained essentially the same taste over the 91-day period, the nasogastric suspension became more bitter by day 49; the taste remained stable from then until the end of the study. The suspensions were easily resuspended throughout the study period. No significant fluctuations in pH were observed. The mean pH (± standard deviation) was 8.75 ± 0.25 and 8.71 ± 0.25, respectively, for the 3 mg/mL nasogastric suspension stored at 4°C and 25°C, and 8.84 ± 0.16 and 8.82 ± 0.17 for the oral suspension stored at 4°C and 25°C.



The HPLC analysis showed that, at both storage temperatures, the 3 mg/mL suspensions maintained between 90.0% and 110.5% of their initial concentrations on every study day (Table 1). Furthermore, more than 95% of the initial lansoprazole concentration remained on day 91, according to linear regression analysis of the concentration–time data. In addition, the calculated lower limit of the 95% CI also indicated that 90% (specifically 89.64%) or more of the initial concentration remained on day 91 (Table 1).

## DISCUSSION

The lack of a commercially available suspension of lansoprazole in Canada poses a problem for children and adults who are unable to swallow solid dosage forms. Until the time of this study, lansoprazole suspensions had been extemporaneously prepared at the authors' institution in 8.4% NaHCO<sub>3</sub> and given an expiry date of only 4 weeks. Although this formulation was satisfactory for nasogastric administration, its salty and bitter taste rendered it unpalatable for oral administration. The commercially available sweetening and suspending agents, Ora-Sweet and Ora-Plus, respectively, have gained popularity in recent years. However, the stability of oral lansoprazole formulations made with these agents was unknown.

Lansoprazole presented a particular challenge because it is a weak base and acid labile. The rationale for preparing lansoprazole in an alkaline (pH of about 8.4) suspension (i.e., in 8.4% NaHCO<sub>3</sub>) was not only to dissolve the enteric coating but also to neutralize gastric acid, thus maintaining a neutral milieu and preventing intraluminal protonation of the lansoprazole and

degradation of the intact drug. However, the pH of 1:1 Ora-Sweet and Ora-Plus, as tested in the authors' laboratory, was only 4.25. Preliminary tests showed that a suspension made with Ora-Sweet and Ora-Plus and buffered to an alkaline pH of about 8.4 with NaHCO<sub>3</sub> was unpalatable. On the other hand, a similar suspension buffered with NaOH instead was deemed acceptable. For some pharmacies, NaOH is less readily available than NaHCO<sub>3</sub>, but the therapeutic advantage of improved pediatric palatability and compliance outweighs this compounding inconvenience.

In the weekly analysis of samples in this study, no notable changes in pH, odour, or colour were observed in suspensions of either the nasogastric or the oral formulation after storage at 4°C or 25°C for 91 days. Although the oral suspension maintained essentially the same taste over the 91-day period, the nasogastric suspension developed a more bitter taste by day 49, but the taste then remained stable until the end of the study. Precipitates were easily resuspended, and there was no caking or clumping of material. Both the nasogastric and the oral formulations of lansoprazole maintained at least 90% of initial concentration at both temperatures in glass bottles throughout the 91-day period.

The findings reported here contrast with those of a previous study, in which a lansoprazole suspension (3 mg/mL) was stable for only 8 h when prepared from capsule contents mixed in 100 mL of 8.4% NaHCO<sub>3</sub> and stored at room temperature (22°C) in amber-coloured, plastic oral syringes.<sup>9</sup> The refrigerated (4°C) samples in that study were stable for only 14 days, whereas the refrigerated samples in the current study were stable for 91 days. The different storage containers (plastic syringes and glass bottles, respectively) may account for

**Table 1. Mean Lansoprazole Concentration ± Standard Deviation (and Mean Percentage Remaining from Initial Concentration\*) during 91 Days of Storage in Glass Bottles at 4°C and 25°C**

Study day	Nasogastric Formulation (in NaHCO <sub>3</sub> 8.4%), 3.0 mg/mL†		Oral Formulation (in NaHCO <sub>3</sub> 8.4% in OS-OP, adjusted with NaOH), 3.0 mg/mL†	
	4°C	25°C	4°C	25°C
0	3.223 ± 0.251	3.103 ± 0.043	2.886 ± 0.109	2.999 ± 0.129
7	3.094 ± 0.017 (96.0)	2.840 ± 0.177 (91.5)	2.949 ± 0.599 (102.2)	2.719 ± 0.144 (90.7)
14	2.971 ± 0.385 (92.2)	2.853 ± 0.266 (91.9)	2.919 ± 0.406 (101.1)	3.062 ± 0.825 (102.1)
21	3.084 ± 0.042 (95.7)	3.054 ± 0.326 (98.4)	3.060 ± 0.247 (106.0)	2.817 ± 0.253 (93.9)
28	3.104 ± 0.448 (96.3)	2.910 ± 0.199 (93.8)	2.740 ± 0.427 (94.9)	2.747 ± 0.333 (91.6)
35	3.449 ± 0.554 (107.0)	3.138 ± 0.214 (101.1)	2.740 ± 0.163 (94.9)	3.052 ± 0.210 (101.8)
42	3.155 ± 0.381 (97.9)	3.109 ± 0.280 (100.2)	2.787 ± 0.188 (96.6)	2.816 ± 0.097 (93.9)
49	3.265 ± 0.288 (101.3)	3.104 ± 0.236 (100.0)	2.854 ± 0.186 (98.9)	2.720 ± 0.171 (90.7)
56	3.412 ± 0.267 (105.9)	3.123 ± 0.318 (100.6)	2.917 ± 0.159 (101.1)	2.764 ± 0.228 (92.2)
63	3.408 ± 0.167 (105.7)	3.184 ± 0.121 (102.6)	2.821 ± 0.488 (97.7)	2.758 ± 0.076 (92.0)
70	3.294 ± 0.083 (102.2)	3.165 ± 0.167 (102.0)	3.031 ± 0.276 (105.0)	2.785 ± 0.190 (92.9)
77	3.188 ± 0.054 (98.9)	3.011 ± 0.160 (97.0)	3.189 ± 0.052 (110.5)	3.085 ± 0.343 (102.9)
84	3.014 ± 0.186 (93.5)	3.238 ± 0.183 (104.4)	3.073 ± 0.232 (106.5)	2.699 ± 0.248 (90.0)
91	3.055 ± 0.349 (94.8)	3.011 ± 0.118 (97.0)	2.710 ± 0.070 (93.9)	3.090 ± 0.133 (103.0)
Coefficient of variation (%)‡	3.98	5.16	3.19	4.42
% remaining on day 91 by linear regression§	98.27	95.54	99.53	95.53
Lower limit of 95% CI for % remaining¶	92.83	91.64	93.88	89.64

NaHCO<sub>3</sub> = sodium bicarbonate, OS-OP = 1:1 mixture of Ora-Sweet sweetening agent and Ora-Plus suspending agent, NaOH = sodium hydroxide, CI = confidence interval.

\*Percentage remaining was calculated in relation to the initial concentration (day zero) for each of the 3 replicate samples stored at each temperature.

†Nominal concentration; note that the original concentration was 3 mg/mL but samples were diluted to 30 µg/mL for analysis.

‡The variability of the estimated percent remaining over the 91-day study period is expressed as the coefficient of variation (standard deviation/mean).

§Calculated from concentration on day 91 as determined by linear regression and concentration observed on day zero, according to the following formula: concentration on day 91/concentration on day zero x 100.

¶Calculated from lower limit of 95% CI of the slope of the curve relating concentration to time, determined by linear regression, according to the following formula: lower limit of 95% CI of concentration on day 91/concentration on day zero x 100.

the difference in stability of lansoprazole suspensions in these 2 studies. That is, a substance present in the plastic syringes but not in the glass might have reduced the stability of lansoprazole. In addition, the amber syringes used in the previous study would not have protected the lansoprazole from UV light during storage at room temperature. In contrast, the suspension would have been more stable during storage in the refrigerator, where it is naturally dark.

A limitation of the current study design relates to the freezing of the samples at -85°C until the time of batch analysis. It was assumed that lansoprazole would not degrade at this low temperature, and that no volume losses would occur because of freeze-drying during storage. In addition, it was assumed that errors due to serial analysis would have been greater than errors occurring with batch analysis.

In vitro determination of stability of a preparation does not automatically guarantee that pharmacokinetics and pharmacodynamics will remain unchanged in vivo. Ideally, follow-up pharmacokinetic and pharmacodynamic studies should therefore be performed. Such studies have not been performed for the oral formulation used here (suspension 2). However, previous studies have assessed the pharmacokinetics and pharmacodynamics of the nasogastric formulation (suspension 1). Specifically, a previous pharmacokinetic study found that the absorption of lansoprazole was similar when the drug was given as an intact 30-mg capsule and as a "simplified suspension" (i.e., contents of 30-mg capsule in 10 mL of 8.4% NaHCO<sub>3</sub>), whereas the absorption of omeprazole given as capsules was impaired relative to the absorption of suspensions.<sup>7</sup> It is important to note that the lansoprazole suspensions were freshly prepared

in the earlier pharmacokinetic study; results may not be comparable when suspensions are stored under various conditions and for extended periods in practice. Also, in contrast to the 10-mL volume of 8.4% NaHCO<sub>3</sub> administered to adults in the pharmacokinetic study, the small volume of alkaline suspension being administered to children is unlikely to maintain a neutral pH in the stomach and prevent lansoprazole degradation.

A pharmacokinetic–pharmacodynamic study found that the simplified suspension was bioequivalent to the intact capsule and was equally effective at controlling intragastric pH.<sup>10</sup> Again, in that study the lansoprazole suspension (in a 10-mL volume of NaHCO<sub>3</sub>) was freshly prepared and administered to adult subjects. Immediately after administration of the suspension, 30 mL of water was used to flush the nasogastric tube, and subjects were given another 150 mL of water to drink. These relatively large volumes would further dilute the acid present. However, such large volumes of NaHCO<sub>3</sub> or water would probably not be given to children.

A previous pharmacodynamic study showed that lansoprazole, given as non-encapsulated granules in orange juice, effectively suppresses intragastric acidity when administered through a gastrostomy tube<sup>5</sup>; a follow-up study showed that the degree of acid suppression was similar when lansoprazole was administered as a simplified suspension via a gastrostomy tube.<sup>6</sup> The contents of a 30-mg lansoprazole capsule were mixed with 10 mL of 8.4% NaHCO<sub>3</sub>, administered through a gastrostomy tube (within 15 min of preparation of the suspension), and flushed into the gastric lumen with 10 to 15 mL of water.

Because lansoprazole is acid labile, administration of only 1 to 2 mL of the nasogastric or oral formulation may not sufficiently neutralize stomach acid, and hence lansoprazole may be degraded. As such, and because previous studies used freshly made lansoprazole suspensions in a minimum volume of 10 mL of 8.4% NaHCO<sub>3</sub>, pharmacokinetic and pharmacodynamic studies are still needed.

In the meantime, flushing of the nasogastric or gastrostomy tube with (or having the child drink) as much water as is allowable, after the lansoprazole dose, is recommended to prevent clogging of the tube and degradation of lansoprazole by gastric acid. At the authors' institution, jejunostomy tubes (J tubes) are generally used for children with longer-term need for a feeding tube because of the better absorptive capabilities and tolerance of feeding into the jejunum. The other potential advantage of the J tube for administration of lansoprazole suspensions is that it bypasses the stomach and degradation of the lansoprazole by gastric acid would thus be prevented. At the authors' institution,

initiation of proton pump inhibitor (e.g., lansoprazole) overlapped with 7 days of histamine<sub>2</sub>-receptor antagonist (H<sub>2</sub>-RA) therapy (e.g., ranitidine 4 to 6 mg/kg per day orally, divided into 2 or 3 doses) is recommended to optimize absorption and help ensure acid suppression. In theory, the effects of the proton pump inhibitor itself should then decrease acidity and allow increased absorption of the suspension in subsequent doses. Others have also recommended that an antacid (2 h before the proton pump inhibitor dose) or an H<sub>2</sub>-RA (15 to 20 min before the proton pump inhibitor dose) be given for the first week of therapy to prevent degradation of proton pump inhibitors in gastric acid.<sup>13</sup>

In summary, according to qualitative, pH, and HPLC analysis of weekly samples, lansoprazole suspensions of 3 mg/mL stored at either 4°C or 25°C remained stable and maintained at least 90% of their original concentrations in glass bottles for up to 91 days. Thus, the results of this study provide information on extending the expiry date of lansoprazole suspensions for nasogastric administration, as well as new information on the stability of a palatable suspension for oral administration. Future clinical studies are warranted to evaluate the pharmacokinetics and pharmacodynamics of these formulations.

#### References

1. Robinson M, Horn J. Clinical pharmacology of proton pump inhibitors: what the practising physician needs to know. *Drugs* 2003;63(24):2739-2754.
2. Bown RL. An overview of the pharmacology, efficacy, safety and cost-effectiveness of lansoprazole. *Int J Clin Pract* 2002;56(2):132-139.
3. Health Canada approves pediatric indication for Prevacid (lansoprazole) for children with gastroesophageal reflux disease. Doctor's Guide Publishing Ltd; 2005 Feb 10 [cited 2006 Aug 28]. Available from: <http://www.pslgroup.com/dg/24A196.htm>
4. Lansoprazole. In: *Drug product database (DPD)*. Ottawa (ON): Health Canada; [cited 2006 Aug 28]. Available from: [http://search.hc-sc.gc.ca/cgi-bin/query?mss=hc%2Fdpd%2Fenglish%2Factive%2F\\_simple&pg=q&what=web&kl=XX&enc=iso88591&site=main&filter=product&q=lansoprazole](http://search.hc-sc.gc.ca/cgi-bin/query?mss=hc%2Fdpd%2Fenglish%2Factive%2F_simple&pg=q&what=web&kl=XX&enc=iso88591&site=main&filter=product&q=lansoprazole)
5. Sharma VK, Ugheoke EA, Vasudeva R, Howden CW. The pharmacodynamics of lansoprazole administered via gastrostomy as intact, non-encapsulated granules. *Aliment Pharmacol Ther* 1998;12(11):1171-1174.
6. Sharma VK, Vasudeva R, Howden CW. Simplified lansoprazole suspension—a liquid formulation of lansoprazole—effectively suppresses intragastric acidity when administered through a gastrostomy. *Am J Gastroenterol* 1999;94(7):1813-1817.
7. Sharma VK, Peyton B, Spears T, Raufman JP, Howden CW. Oral pharmacokinetics of omeprazole and lansoprazole after single and repeated doses as intact capsules or as suspensions in sodium bicarbonate. *Aliment Pharmacol Ther* 2000;14(7):887-892.
8. Chun AH, Erdman K, Chiu YL, Pilmer BL, Achari R, Cavanaugh JH. Bioavailability of lansoprazole granules administered in juice or soft food compared with the intact capsule formulation. *Clin Ther* 2002;24(8):1322-1331.
9. DiGiacinto JL, Olsen KM, Bergman KL, Hoie EB. Stability of suspension formulations of lansoprazole and omeprazole stored in amber-colored plastic oral syringes. *Ann Pharmacother* 2000;34(5):600-605.



10. Doan TT, Wang Q, Griffin JS, Lukasik NL, O'Dea RF, Pan WJ. Comparative pharmacokinetics and pharmacodynamics of lansoprazole oral capsules and suspension in healthy subjects. *Am J Health Syst Pharm* 2001;58(16):1512-1519.
11. Litalien C, Theoret Y, Faure C. Pharmacokinetics of proton pump inhibitors in children. *Clin Pharmacokinet* 2005;44(5):441-466.
12. Dentinger PJ, Swenson CF, Anaizi NH. Stability of pantoprazole in an extemporaneously compounded oral liquid. *Am J Health Syst Pharm* 2002;59(10):953-956.
13. Fan E, Gavura S, Ruddock B. Proton pump inhibitors in pediatric patients. *Can Pharm J* 2006;139(5):53-55.

**Mary H H Ensom**, PharmD, FASHP, FCCP, FCSHP, is Professor and Director, Doctor of Pharmacy Program, Faculty of Pharmaceutical Sciences and Distinguished University Scholar, The University of British Columbia; and Clinical Pharmacy Specialist, Department of Pharmacy, Children's and Women's Health Centre of British Columbia; Vancouver, British Columbia. She is also the Editor of *CJHP*.

**Diane Decarie**, BSc, is Research Consultant, Department of Pharmacy, Children's and Women's Health Centre of British Columbia, Vancouver, British Columbia.

**Ian Sheppard**, BSc, is Manager, Department of Pharmacy, Children's and Women's Health Centre of British Columbia, Vancouver, British Columbia.

**Address correspondence to:**

Dr Mary H H Ensom  
 Department of Pharmacy (0B7)  
 Children's and Women's Health Centre of British Columbia  
 4500 Oak Street  
 Vancouver BC  
 V6H 3N1

**e-mail:** ensom@interchange.ubc.ca

**Acknowledgements**

We thank Dr. Roxane Carr for her invaluable clinical insights and suggestions, and Paul Koke and Don Hamilton for their assistance in project logistics.

## Appendix 1. Preparation of Nasogastric and Oral Suspensions of Lansoprazole

### Suspension 1: Nasogastric suspension (lansoprazole 3 mg/mL)

1. To prepare sodium bicarbonate (NaHCO<sub>3</sub>) 8.4% 500 mL:
  - To 450 mL water (H<sub>2</sub>O), add 42.0 g NaHCO<sub>3</sub>
  - Dissolve by mixing over the hot plate (37°C) for 15 min
  - Qs ad 500 mL in volumetric flask
2. To prepare 100 mL lansoprazole suspension (30 mg in 10 mL in NaHCO<sub>3</sub> 8.4%):
  - Dissolve the contents of 10 capsules of lansoprazole 30 mg in 100 mL NaHCO<sub>3</sub> 8.4%

### Suspension 2: Oral suspension (lansoprazole 3 mg/mL in Ora-Sweet–Ora-Plus buffered with NaOH)

1. To prepare 50 mL of lansoprazole suspension 6 mg/mL in NaHCO<sub>3</sub> 8.4%:
  - Empty the contents of 10 capsules of lansoprazole 30 mg into 50 mL of NaHCO<sub>3</sub> 8.4%
  - Stir for 15 min at 25°C (room temperature)
2. To prepare 50 mL buffered Ora-Sweet–Ora-Plus:
  - To 45 mL Ora-Sweet–Ora-Plus, add 3.4 mL NaOH (sodium hydroxide) 1N
  - Qs ad 50 mL with Ora-Sweet–Ora-Plus
3. To prepare 50 mL of lansoprazole 3 mg/mL in Ora-Sweet–Ora-Plus buffered with NaOH:
  - To 25 mL of buffered Ora-Sweet–Ora-Plus, add 25 mL of lansoprazole suspension 6 mg/mL in NaHCO<sub>3</sub> 8.4%

### Suspension 3: Oral suspension (lansoprazole 3 mg/mL in Ora-Sweet–Ora-Plus buffered with NaHCO<sub>3</sub>)

1. To prepare 50 mL of lansoprazole suspension 6 mg/mL in NaHCO<sub>3</sub> 8.4%:
  - Empty the contents of 10 capsules of lansoprazole 30 mg into 50 mL of NaHCO<sub>3</sub> 8.4%
  - Stir for 15 min at 25°C (room temperature)
2. To prepare 50 mL buffered Ora-Sweet–Ora-Plus:
  - To 45 mL Ora-Sweet–Ora-Plus, add 13 g NaHCO<sub>3</sub> powder and mix
  - Qs ad 50 mL with Ora-Sweet–Ora-Plus
3. To prepare 50 mL of lansoprazole 3 mg/mL in Ora-Sweet–Ora-Plus buffered with NaHCO<sub>3</sub>:
  - To 25 mL of buffered Ora-Sweet–Ora-Plus, add 25 mL of lansoprazole suspension 6 mg/mL in NaHCO<sub>3</sub> 8.4%

